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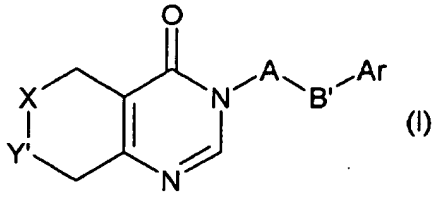
New 3-substituted tetrahydropyridopyrimidinone derivatives C1999-099738

Addnl. Data: LUBISCH W, DULLWEBER U, STARCK D, STEINER G, BACH A, EMLING F, GARCIA-LADONA F J, TESCHENDORF H, WICKE K

B(6-D8, 14-E10, 14-J1A, 14-J4, 14-L6) .4



(I)

One of X and Y = CH_2 and the other = NR^1;
R^1 = H, 1-6C alkyl, (1-4C alkyl)carbonyl, CO_2-tert.-butyl, arylcarbonyl or phenyl-(1-4C alkyl), which may itself be ring-substituted by F, Cl, Br, I, 1-4C alkyl, 1-4C alkoxy, CF_3, OH, NH_2, CN or NO_2;
A = 1-10C alkylene or 2-10C alkylene containing one or more Z groups;
Z = O, S, NR^2, cyclopropyl, CO_2, CHOH, or a double or triple bond;
R^2 = H or 1-4C alkyl;
B' = 4-piperidine, 4-(1,2,3,6-tetrahydropyridine), 4-piperazine or one of these rings N-bound to A via a methylene group;
Ar = phenyl (optionally substituted by 1-6C alkyl, 1-6C alkoxy, OH, F, Cl, Br, I, CF_3, $N(R^2)_2$, CO_2R^2, CN or phenyl), tetralinyl, indanyl, other condensed aromatic moieties e.g. naphthalinyl (optionally substituted by 1-4C alkyl or 1-4C alkoxy), anthracenyl, or a 5- or 6-membered aromatic heterocycle with 1 or 2 O or N heteroatoms, which can be anellated with other aromatic groups.

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NOVELTY

3-Substituted tetrahydropyridopyrimidinone derivatives (I) and their acid salts are new.

DETAILED DESCRIPTION

3-Substituted tetrahydropyridopyrimidinone derivatives of formula (I) and their acid salts are new.

ACTIVITY

Antidepressant; Nootropic; Tranquilizer; Vasodilator; Cerebroprotective; Relaxant.

MECHANISM OF ACTION

5-HT_1B antagonist; 5-HT1A antagonist (claimed).

USE

(I) are useful for treatment of depression (claimed). The compounds can also be used to treat other disorders such as seasonal affective disorder, dysthymia, anxiety, panic attacks, obsessive-compulsive disorder, social phobia, post traumatic stress syndrome, dementia, amnesia, anorexia nervosa and bulimia nervosa. (I) can also be used to treat sexual dysfunction, hyperprolactinemia, blood vessel spasms (especially in the brain), hypertonia and gastrointestinal diseases associated with abnormal motility and secretion.

ADVANTAGE

Compounds (I) have high affinity for 5-HT_1B, 5-HT1D and 5-HT1A serotonin receptors combined with very little influence on other types of receptor. The compounds' affinity for these receptors is more or less equal, or at least of the same order of magnitude; as a result, they show a good level of serotonin re-uptake inhibition which is of importance in treating depression.

SPECIFIC COMPOUNDS

Over 550 compounds (I) are specifically disclosed, e.g. 3-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-3,5,7,8-tetrahydro-4-oxo-6-benzylpyrido[4,3-d]pyrimidine (Ia).

ADMINISTRATION

Daily dose is 1-100 mg/kg orally and 0.1-10 mg/kg parenterally.

EXAMPLE

To a solution of 2.4 g (10 mmol) tetrahydropyridopyrimidine in

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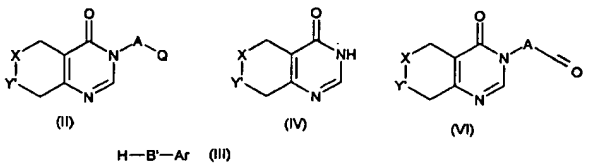
40 ml DMF was added 2.9 g (10 mmol) chloroethylpiperazine and 2.8 g (20 mmol) potassium carbonate. The mixture was allowed to react for two hours at 90 °C and was then poured onto ice/water and extracted with acetic acid ester. The organic phase was washed with saturated NaCl solution and dried over sodium sulfate, and the solvent was removed under vacuum. The oily residue was mixed with acetone and converted to the hydrochloride by adding isopropanol/HCl. The yield of (Ia) hydrochloride was 4 g (75 %).

TECHNOLOGY FOCUS

Organic Chemistry - Preparation: (I) are prepared by: (4) Reacting a compound of formula (II) with a compound of formula H-B-Ar (III) (5) Reacting a compound of formula (IV) with one of formula Q-A-B-Ar (V) (6) Coupling of a compound of formula (VI) with (III) by reductive amination.



(II) (IV) (VI)

H—B'—Ar (III)

Q = a cleavable group e.g. Cl, Br, I, alkanesulfonyloxy or arylsulfonyloxy.
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